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U S DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
40999

U.S. APPLICATION NO. (if known, see 37 C F R 1 5)
10/088884

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/28713	**17 October 2000**	**18 October 1999**

TITLE OF INVENTION
AMINOALKYLENEPHOSPHONATES FOR TREATMENT OF BONE DISORDERS

APPLICANT(S) FOR DO/EO/US
R. Keith Frank

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [X] is not required, as the application was filed in the United States receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the Annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 15. below concern other document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
13. [ ] A substitute specification.
14. [ ] A change of power of attorney and/or address letter.
15. [ ] Other items or information:

U.S. APPLICATION NO. (If known, see 37 C F.R 1.50)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/038884	PCT/US00/28713	40999

17. ☒ The following fees are submitted:		CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)):			
Search Report has been prepared by the EPO or JPO	$ 890.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482)	$ 710.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))	$ 740.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445 (a)(2)) paid to USPTO	$ 1,040.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$ 100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =		$ 890.00	
Surcharge of $ 0.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	+	$ 0.00	

Claims	Number Filed	Number Extra	Rate		
Total Claim	18 - 20 =	0	X $ 18.00	$ 0.00	
Independent Claims	2 - 3 =	0	X $ 84.00	$ 0.00	
Multiple dependent claim(s) (if applicable)			$ 0.00	$ 0.00	
Processing fee of $ 0 for furnishing the English Translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).			+	$ 0.00	
			TOTAL NATIONAL FEE =	$ 890.00	
				Amount to be refunded:	$
				charged:	$

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **04-1512** in the amount of $ **890.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **04-1512** . A duplicate copy of this sheet is enclosed.

Note: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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Date: **21 March 2002**

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THIS APPLICATION IS THE ENTRY INTO THE NATIONAL PHASE UNDER 35 U.S.C. 371

Applicant(s): THE DOW CHEMICAL COMPANY

International Application No. PCT/US00/28713

International Filing Date: 17 October 2000

Priority Date Claimed: 18 October 1999

Title: AMINOALKYLENEPHOSPHONATES FOR TREATMENT OF BONE DISORDERS

Attorney's Docket No.: 40999

AMINOALKYLENEPHOSPHONATES FOR TREATMENT OF BONE DISORDERS

This invention relates to the use of aminoalkylenephosphonates for treatment of bone disorders such as osteoporosis.

This invention involves the use of aminoalkylenephosphonates, such as, for example, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylenephosphonic acid (DOTMP) and 3,6,9,15-tetraazabicyclo[9.3.1]tetradeca-1(15),11,13-triene-3,6,9-trimethylenephosphonic acid (PCTMP) for use in the inhibition of bone resorption. This application is directed toward use in the prevention and/or treatment of bone diseases such as osteoporosis. Bone is a dynamic tissue, continually undergoing remodeling. Hydroxyapatite, the main inorganic constituent of bone, is constantly being deposited and resorbed. In pathological states such as osteoporosis a shift in the balance of these two processes occurs, resulting in a net loss of mineralized tissue. This loss results in impaired skeletal function and clinical fractures. Osteoporosis is an enormous public health problem affecting as many as 25 million people in the United States alone. It is a pervasive disease that has staggering costs to society in terms of morbidity, mortality, and economics. As the population becomes more aged, the magnitude of this problem will certainly become greater.

Currently only three drugs - estrogen, calcitonin, and alendronate are approved by the FDA for use in the treatment of osteoporosis. Both estrogen and calcitonin have some drawbacks (for example, estrogen - risk of endometrial carcinoma, calcitonin - allergic reaction) and are not always successful. The recently approved

bisphosphonate alendronate (4-amino-1-hydroxybutylidenebisphosphonate) is a member of a class of compounds that has received much attention for their potential in treating bone-related illnesses.

Bisphosphonates all contain the basic P-C-P structure. Examples such as etidronate (1-hydroxy-ethylidenebisphosphonate), risedronate [1-hydroxy-2-(3-pyridinyl)ethylenebisphosphonate], pamidronate (3-amino-1-hydroxypropylidenebisphosphonate), tiludronate (4-chlorophenylthiomethylenebisphosphonate) have already been approved for the treatment of a rare bone condition called Paget's disease.

Aminoalkylenephosphonates have not been investigated for these applications. It is known that these compounds have a strong affinity for bone (for example, EDTMP and DOTMP radiopharmaceutical bone agents) and have low soft tissue localization. They have unique properties such as the ability to inhibit calcium phosphate scale formation at very low concentrations.

It has now been discovered that aminoalkylene-phosphonates can inhibit bone mineral density loss. In fact, a screening study of various aminomethylene-phosphonates in an ovarectomized rat osteoporosis model has now shown that PCTMP is as good as, and may even be superior to, alendronate in its ability to inhibit bone mineral loss.

The present invention relates to a method for preventing or minimizing loss of bone mineral in mammals which method comprises administering to a mammal an amount of an aminoalkylenephosphonate which is effective to prevent or minimize loss of bone mineral density.

In another aspect, the present invention relates to the use of an aminoalkylenephophonate or a pharmaceutically acceptable salt thereof in the manufacture of a pharmaceutical formulation for preventing or minimizing loss of bone mineral in mammals.

The term "aminoalkylenephosphonate" as used herein refers to those phosphonates and phosphonic acids which incorporate an amine moiety, whether aliphatic or cyclic, attached via the amine nitrogen through an alkylene group to the phosphonate or phosphonic acid moiety. The aminoalkylenephosphonates of the present invention should have at least one $R-N(Alk-PO_3H_2)_2$ group or at least two $RR'N-Alk-PO_3H_2$ groups wherein R and R' can be, same or different, aliphatic or cyclic moiety, and Alk is an alkylene group having from 1 to 4 carbon atoms.

The amine moiety of the aminoalkylenephosphonates of the present invention represented by the R-N= and RR'N- in the aforementioned $R-N(Alk-PO_3H_2)_2$ and $RR'N-Alk-PO_3H_2$ groups is derived from either an aliphatic or a cyclic polyamine in which hydrogen atoms bonded to the nitrogen atom(s) in the amine moiety are partially or completely substituted by an alkylphoshonate group. Non-limiting examples of the amines suitable as amine moieties in the practice of the present invention are ethylenediamine (EDA), diethylenetriamine (DETA), triethylenetetraamine (TETA), 1,4,7,10-tetraazacyclododecane, 3,6,9,15-tetraaza-bicyclo[9.3.1]tetradeca-1(15),11,13-triene, 2,11-diaza[3.3](2,6)pyridinophane, 2-(aminomethyl)pyridine, 2,6-bis(aminomethyl)pyridine.

The alkylene group having from 1 to 4 carbon atoms contemplated by Alk in the aforementioned formulas can be straight or branched chain alkylene group. Non-limiting examples of such alkylene groups are methylene, ethylene,

propylene, isopropylene, and butylene. The preferred alkylene group is methylene ($-CH_2-$) group.

Preferred aminoalkylenephosphonates are aminomethylenephosphonates. Particularly preferred aminoalkylenephosphonates are 1,4,7,10-tetraaza-cyclododecane-1,4,7,10-tetramethylenephosphonic acid (DOTMP), 3,6,9,15-tetraazabicyclo[9.3.1]tetradeca-1(15),11,13-triene-3,6,9-trimethylenephosphonic acid (PCTMP), N,N'-bis(methylenephosphonic acid)-2,11-diaza[3.3](2,6)pyridinophane (BP2MP) and N,N-bis(methylene phosphonic acid)-2-(aminomethyl)pyridine (AMPDMP).

The aminoalkylenephosphonates contemplated by the present invention are well known in the art and numerous methods for their preparation have been disclosed. See, for example, U.S. Patent No. 3,288,846 (Irani et al) and U.S. Patent No. 4,898,724 (Simon et al), both incorporated herein by reference.

The aminoalkylenephosphonates of the present invention are used in an amount effective to prevent or minimize loss of bone mineral. The effective amount will vary depending on the mammal, aminoalkylenephosphonate used and the method of its administration (for example, oral or parenteral). A person of ordinary skill in the art will know how to determine the effective amount of aminoalkylene-phosphonate.

The aminoalkylenephosphonates of the present invention can be administered to a mammal on a daily or weekly regiment basis. Typically, for average 50 kg mammal, the effective weekly parenteral dose is in the range of from about 0.01 mg to about 500 mg, preferably from about 0.1 mg to about 250 mg, most preferably from about 0.1 to about 70 mg. Typically, for average 50 kg

mammal, the effective daily oral dose is in the range of from about 0.1 mg to about 40 g, preferably from about 0.1 mg to about 10 g, most preferably from about 0.1 to about 5 g.

In the practice of the present invention the aminoalkylenephosphonate may be administered per se or as a component of a pharmaceutically acceptable composition.

Thus, the present invention may be practiced with the aminoalkylenephosphonate being provided in pharmaceutical formulation, both for veterinary and for human medical use. Such pharmaceutical formulations comprise the active agent (the aminoalkylenephosphonate) together with one or more pharmaceutically acceptable carriers thereof and optionally any other therapeutic ingredients. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredient(s) in the formulation and not unsuitably deleterious to the recipient thereof. The aminoalkylenephosphonate is provided in an effective amount, as described above, and in a quantity appropriate to achieve the desired dose.

The formulations include those suitable for oral, rectal, topical, nasal, ophthalmic, or parenteral (including subcutaneous, intramuscular, and intravenous) administration. Formulations may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing the aminoalkylenephosphonate into association with a carrier, which constitute one or more accessory ingredients. In general, the formulation may be prepared by uniformly and intimately bringing the aminoalkylenephosphonate into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product into desired formulation. In addition, the formulations of this

invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavoring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives.

The following Examples are provided to illustrate the present invention, and should not be construed as limiting thereof.

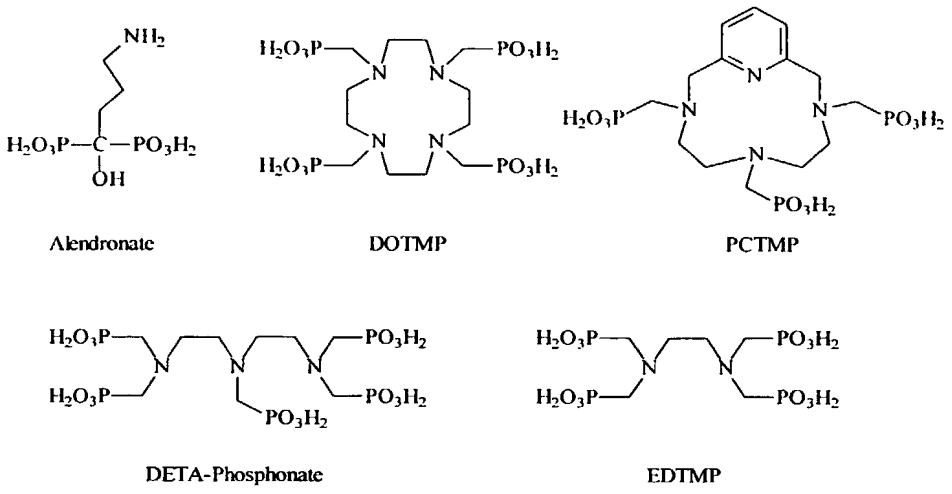
Example 1

Eleven week old Female Sprague-Dawley laboratory rats (75) were fed a commercial rat diet and were allowed to drink water ad libitum. They were housed in pairs in an air-conditioned environment, and were allowed to enjoy 14 hours of illumination per day. Ten rats were sham-operated and were used as "non-osteopenic" control rats. All of the other rats were ovariectomized at 12 weeks of age. All surgeries were done under injectable anesthesia. Ten of the ovariectomized rats were used as an "osteopenic but non-treated" control, and did not receive any phosphonate treatments. The remaining rats were given various phosphonate compounds in groups of ten.

Phosphonates (5 mg/kg) were administered subcutaneously (to insure better bioavailability). The rats were given doses three times during the first week and once a week thereafter.

Structures of the compounds tested are shown below in Figure 1.

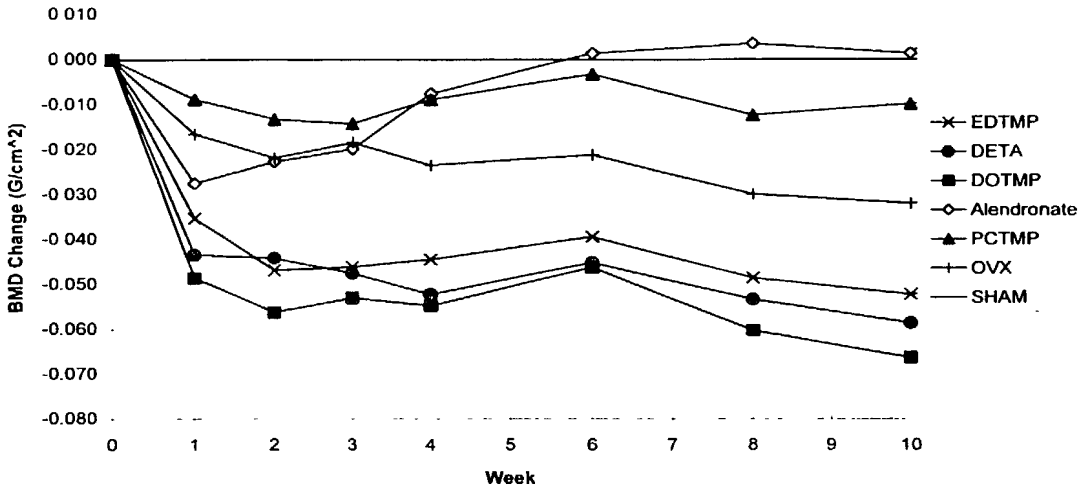
Figure 1. Structures of Compounds Tested (Example 1)



Bone mineral density was determined by single photon absorptiometry while the rats were under injectable anesthesia. The distal femoral metaphysis of all rats were scanned at weekly intervals for ten weeks.

Figure 2 below shows the average drop in bone mineral density, normalized to the sham-operated control group, for the ovariectomized (OVX) control group and for the treatment groups.

Figure 2. Average Change in BMD
(Normalized to sham-operated control = 0)



As can be seen, relative to the sham-operated control, the OVX group loses bone mineral density (BMD) over time. Three aminomethylenephosphonates, DOTMP, EDTMP, and DETA-Phosphonate, all lost more BMD than the OVX group (at this dose level). Both the alendronate and PCTMP groups maintained BMD. (Because of the difference in molecular weight, PCTMP was actually used at a lower dose level than alendronate on a mole basis.)

By week 10, there are three statistical groupings. The sham operated controls, alendronate, and PCTMP are all statistically equivalent. The ovariectomized controls are in a group by themselves, as are the other three aminomethylenephosphonates.

Example 2:

A second study was undertaken to explore the effect of structural changes in PCTMP. The structures of the compounds tested are shown below in Figure 3. Included in the study was DOTMP at one tenth the dose, that is, 0.5 mg/kg. All other compounds were dosed at 5 mg/kg. In this study, bone mineral density was determined by dual energy X-ray absorptiometry (DEXA). Other aspects of the study were substantially the same as in Example 1. The results of the study are shown in Figure 4 below.

Again, it can be seen that, relative to the sham-operated controls, the OVX control group lost significant BMD over the study period. As before, PCTMP shows an improvement over the OVX group. AMPDMP and BP2MP both look even better, but the best compound tested was DOTMP at 0.5 mg/kg. At this dose level it was equivalent to the sham-operated control.

Figure 3. Structures of Compounds Tested

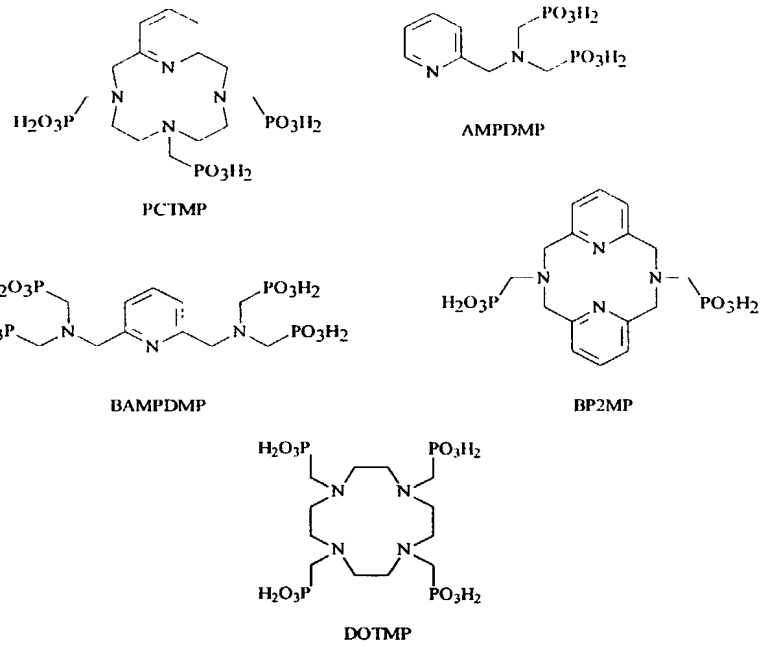
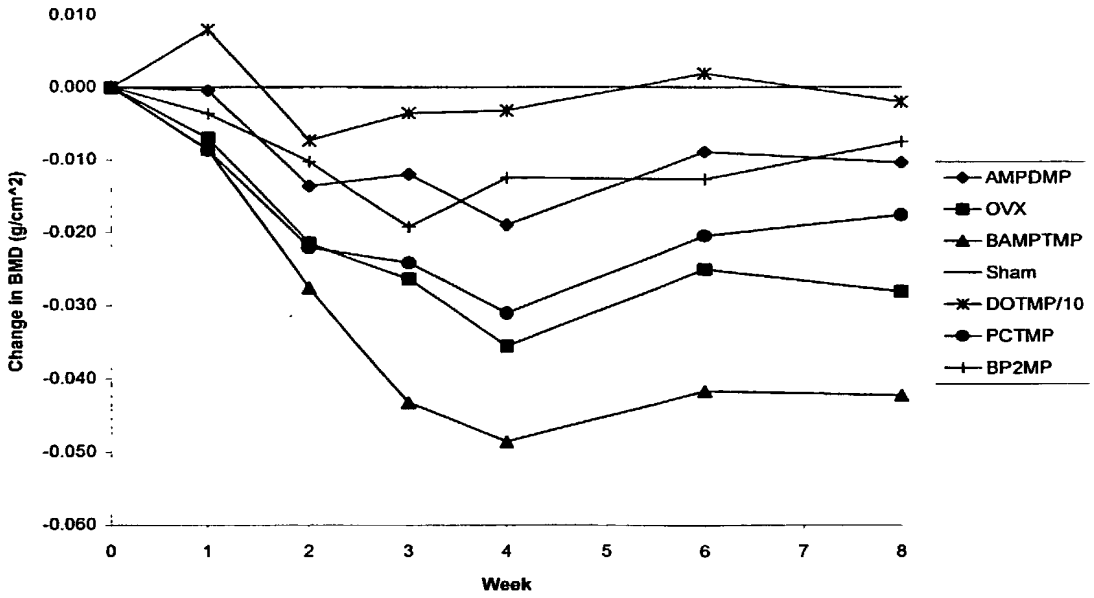


Figure 4. Average Change in BMD
(Normalized to sham-operated control = 0)



WHAT IS CLAIMED IS:

1. A method for preventing or minimizing loss of bone mineral in mammals which method comprises administering to a mammal an amount of an aminoalkylenephosphonate or a pharmaceutically acceptable salt thereof which is effective to prevent or minimize loss of bone mineral density.

2. The method according to Claim 1 wherein said aminoalkylenephosphonate has at least one $R\text{-}N(Alk\text{-}PO_3H_2)_2$ group wherein R can be an aliphatic or cyclic moiety, and Alk is an alkylene group having from 1 to 4 carbon atoms.

3. The method according to Claim 1 wherein said aminoalkylenephosphonate has at least two $RR'N\text{-}Alk\text{-}PO_3H_2$ groups wherein R and R' can be, same or different, aliphatic or cyclic moiety, and Alk is an alkylene group having from 1 to 4 carbon atoms.

4. The method according to Claim 2 or Claim 3 wherein the amine moiety of the aminoalkylenephosphonate represented by the R-N= and RR'N- in the $R\text{-}N(Alk\text{-}PO_3H_2)_2$ and $RR'N\text{-}Alk\text{-}PO_3H_2$ groups is derived from either an aliphatic or a cyclic polyamine in which hydrogen atoms bonded to the nitrogen atoms in the amine moiety are partially or completely substituted by an alkylphoshonate group.

5. The method according to Claim 1 wherein said aminoalkylenephosphonate is an aminomethylenephosphonate.

6. The method according to Claim 1 wherein said aminoalkylenephosphonate is 3,6,9,15-tetraazabicyclo[9.3.1]tetradeca-1(15),11,13-triene-3,6,9-trimethylenephosphonic acid (PCTMP).

7. The method according to Claim 1 wherein said aminoalkylenephosphonate is 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylenephosphonic acid (DOTMP).

8. The method according to Claim 1 wherein said aminoalkylenephosphonate is N,N'-bis(methylenephosphonic acid)-2,11-diaza[3.3](2,6)pyridinophane (BP2MP).

9. The method according to Claim 1 wherein said aminoalkylenephosphonate is N,N-bis(methylenephosphonic acid)-2-(aminomethyl)pyridine (AMPDMP).

10. The use of an aminoalkylenephophonate or a pharmaceutically acceptable salt thereof in the manufacture of a pharmaceutical formulation for preventing or minimizing loss of bone mineral in mammals.

11. The use of an aminoalkylenephophonate or a pharmaceutically acceptable salt thereof according to Claim 10 wherein said aminoalkylenephosphonate has at least one $R\text{-}N(Alk\text{-}PO_3H_2)_2$ group wherein R can be an aliphatic or cyclic moiety, and Alk is an alkylene group having from 1 to 4 carbon atoms.

12. The use of an aminoalkylenephophonate or a pharmaceutically acceptable salt thereof according to Claim 10 wherein said aminoalkylenephosphonate has at least two $RR'N\text{-}Alk\text{-}PO_3H_2$ groups wherein R and R' can be, same or different, aliphatic or cyclic moiety, and Alk is an alkylene group having from 1 to 4 carbon atoms.

13. The use of an aminoalkylenephophonate or a pharmaceutically acceptable salt thereof according to Claim 11 or Claim 12 wherein the amine moiety of the

aminoalkylenephosphonate represented by the R-N= and RR'N- in the $R-N(Alk-PO_3H_2)_2$ and $RR'N-Alk-PO_3H_2$ groups is derived from either an aliphatic or a cyclic polyamine in which hydrogen atoms bonded to the nitrogen atoms in the amine moiety are partially or completely substituted by an alkylphoshonate group.

14. The use of an aminoalkylenephophonate or a pharmaceutically acceptable salt thereof according to Claim 10 wherein said aminoalkylenephosphonate is an aminomethylenephosphonate.

15. The use of an aminoalkylenephophonate or a pharmaceutically acceptable salt thereof according to Claim 10 wherein said aminoalkylenephosphonate is 3,6,9,15-tetraazabicyclo[9.3.1]tetradeca-1(15),11,13-triene-3,6,9-trimethylenephosphonic acid (PCTMP).

16. The use of an aminoalkylenephophonate or a pharmaceutically acceptable salt thereof according to Claim 10 wherein said aminoalkylenephosphonate is 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylenephosphonic acid (DOTMP).

17. The use of an aminoalkylenephophonate or a pharmaceutically acceptable salt thereof according to Claim 10 wherein said aminoalkylenephosphonate is N,N'-bis(methylenephosphonic acid)-2,11-diaza[3.3](2,6)pyridinophane (BP2MP).

18. The use of an aminoalkylenephophonate or a pharmaceutically acceptable salt thereof according to Claim 10 wherein said aminoalkylenephosphonate is N,N-bis(methylenephosphonic acid)-2-(aminomethyl)pyridine (AMPDMP).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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Published:
— *Without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: AMINOALKYLENEPHOSPHONATES FOR TREATMENT OF BONE DISORDERS

(57) Abstract: A method for preventing or minimizing loss of bone mineral in mammals which method comprises administering to a mammal an amount of an aminoalkylenephosphonate which is effective to prevent or minimize loss of bone mineral density. The aminoalkylenephosphonates of the present invention should have at least one R-N(Alk-PO_3H_2)$_2$ group or at least two RRN-Alk-PO_3H_2 groups wherein R and R can be, same or different, aliphatic or cyclic moiety, and Alk is an alkylene group having from 1 to 4 carbon atoms.

DECLARATION AND POWER OF ATTORNEY

USA/PCT

As a below named inventor, I hereby declare that:

(a) My residence and Citizenship are as stated below my name. My P O (mailing) address is the same as my residence unless otherwise stated

(b) I verily believe I am/we are the original, first and sole/joint inventor(s) of the subject matter that is embraced by and for which a patent is sought on the invention entitled: **AMINOALKYLENEPHOSPHONATES FOR TREATMENT OF BONE DISORDERS** and the specification of which. ☐ is attached hereto (_____)
(check one) ☒ was filed on October 17, 2000 as (40999)
Application No PCT/US00/28713
and was amended on _____

(c) I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above

(d) I acknowledge my duty under 37 CFR 1.56 to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in 37 CFR 1 56(b) If this application is a continuation-in-part application, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 CFR 1 56(b) that became available between the filing date of the prior application from which priority is claimed in part (f) below, and the national or PCT international filing date of this application.

(e) I hereby claim foreign priority benefits under 35 U S C § 119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below or §365(a) of any PCT international application that designated at least one country other than the United States of America listed below, and also identify below any other foreign equivalent application for patent or inventor's certificate or any other equivalent PCT international application having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN APPLICATION(S)			PRIORITY CLAIMED	CERTIFIED COPIES INCL.
Number	**Country or PCT**	**Day/Month/Year Filed**		
			☐	☐

☐ Additional claims for benefit are attached

(f) I hereby Claim the benefit under 35 U S C §119(e) of any United States provisional application(s) listed below, or under 35 U S C §120 of any United States application(s), or under § 365(c) of any PCT international application designating the United States of America listed below:

US or PCT Appln. Serial No.	Filing Date	Status at Application Filing Date
60/160,019	October 18, 1999	Abandoned

☐ Additional claims for benefit are attached.

I hereby appoint the attorney(s) and/or agent(s) at the following Customer No to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. Address all correspondence to The Dow Chemical Company's appointed counsel at

00109
PATENT TRADEMARK OFFICE

This appointment, including the right to delegate this appointment, shall also apply to the same extent it is applicable under the laws of the United States of America to any proceedings established by the Patent Cooperation Treaty.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under 18 U.S.C § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Inventor(s).

At: Freeport, Texas 77541, USA
this 2nd day of November, 2000

1-00 Signature: R. Keith Frank
Full Name: R. Keith Frank
Residence: 213 Pansy Path
Lake Jackson, Texas 77566 TX
Country: United States of America
Citizenship: United States of America
P. O Address: Same as Residence

At: _____
this ____ day of _____, 20___

Signature: _____
Full Name.
Residence:

Country:
Citizenship
P O Address:

At: _____
this ____ day of _____, 20____

Signature: _____
Full Name.
Residence:

Country:
Citizenship:
P. O. Address:

At: _____
this _____ day of _____, 20____

Signature: _____
Full Name
Residence:

Country:
Citizenship:
P. O. Address:

☐ Additional names and signatures are attached.